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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/668,641	09/23/2003	Yasuharu Hakamazuka	17039	2057

23389 7590 05/18/2007
SCULLY SCOTT MURPHY & PRESSER, PC
400 GARDEN CITY PLAZA
SUITE 300
GARDEN CITY, NY 11530

EXAMINER	
FORD, ALLISON M	
ART UNIT	**PAPER NUMBER**
1651	

MAIL DATE	DELIVERY MODE
05/18/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/668,641	HAKAMAZUKA ET AL.	
	Examiner	Art Unit	
	Allison M. Ford	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-10,13-15,20-25 and 27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-10,13-15,20-25 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response of 20 February 2007 has been received and entered into the case. Claims 8, 9, 13, 14, 20-23, 25 and 27 have been amended; claims 1-7, 11, 12, 16-19 and 26 have been cancelled; no new claims have been added. Claims 8-10, 13-15, 20-25 and 27 remain pending in the current application, all of which have been considered on the merits. All arguments have been fully considered.

Priority

Acknowledgment is made of applicant's claim for priority under 35 U.S.C 365(c) as a continuation of PCT/JP02/02744, filed 22 March 2002, which further claims priority to Japanese national application 2001-084525, filed 23 March 2001. A certified copy of the priority document has been received.

Response to Arguments

Applicants' arguments filed 20 February 2007 have been fully considered. Each argument will be addressed below, as appropriate. Rejections not repeated below have been withdrawn from the record.

With regards to the rejections under 35 USC 112, second paragraph, as being indefinite, applicants have kindly amended the claims to clarify the language as requested. The rejections are withdrawn.

With regards to the rejections under 35 USC 102(b) over each of Bucholz and Erbe *et al*, it is noted applicants have provided a certified copy of a translation of the Japanese national application, filed 23 March 2001, thereby antedating both Bucholz and Erbe *et al*. These rejections are withdrawn.

With regards to the rejections under 35 USC 103(a) over de Bruijn et al (EP 0987032), in view of Hakamazuka et al (JP 01-108143), Muschler (WO 99/59500), and Klein-Nulend et al (J Cell Physiol, 1995), applicants have traversed the rejection on the grounds that the obviousness rationale relied upon by the Examiner was inappropriate. Specifically, applicants argue the claims as amended now require each of the macropores and micropores to constitute a specific disclosed proportion of the total porosity, which they feel is not taught or suggested by the cited art. Additionally, applicants have traversed the Examiner's holding that the claimed pore size ranges are obvious over the pore size ranges recited by de Bruijn et al because de Bruijn et al recite such broad ranges so as to encompass a huge number of compositions, stating that one would not reasonably expect to arrive at the claimed composition, citing *In re Baird* in support. Additionally, applicants have traversed the Examiner's holding that it would have been obvious to add cells to the scaffold of de Bruijn et al, arguing the Examiner has only presented an "obvious to try" argument. Applicants further argue that claim 20 and dependent claims thereof now *optionally* require the use of centrifugal force or applied pressure to incorporate the bone marrow cell, which they argue is not taught or suggested by the applied references. Finally, applicants generally argue that the rejection, as a whole, relies on impermissible hindsight.

Each of these arguments has been fully considered, but none are found persuasive:

In response to Applicants' argument that the amended claims now recite that the micropores and macropores each constitute a specific percentage of the total pore volume, such has been noted, and new grounds of rejection have been made.

In response to Applicants' argument that the pore size ranges disclosed by de Bruijn et al do not render obvious the claimed pore size ranges, it is maintained that because the ranges disclosed by de Bruijn et al lie within the ranges currently claimed, or are otherwise significantly overlapping, it would not be unreasonable to expect the artisan of ordinary skill to successfully optimize these ranges. With regards to the reference to *In re Baird*, it is noted that the fact pattern in *In re Baird* is not similar to the

instant case. The issue at hand in *In re Baird* was whether the claimed diphenol, bisphenol A, would have been an obvious species selection to one of ordinary skill based on the disclosure of the generic diphenol formula disclosed in the Knapp patent, wherein the generic formula encompassed over 100 million different phenols. Unlike in *In re Baird*, the instant rejection was not over obviousness of a species based on disclosure of a genus; rather, the instant rejection is based on the idea that optimization of a workable range would be within the purview of the skilled artisan when the prior art discloses a similar range. It has consistently been held that in cases where the claimed range overlaps or lies within the range recited by the prior art, the applicant must show that the particular range is *critical,* generally by showing that the claimed range achieves unexpected results relative to the prior art range; because applicants have not shown such, the rejections of record stand.

In response to Applicants' arguments that the Examiner only presented "obvious to try" rationale with regards to adding bone marrow cells to the scaffold of de Bruijn et al, it is noted that the rejection relied on Muschler, who successfully incorporated bone marrow aspirate cells into a porous scaffold. It is further submitted that incorporation of cells, specifically bone marrow cells, into scaffolds intended for use as bone grafts, was well known in the art. Thus, based on the success of the prior art, it is respectfully submitted that the motivation was not merely "obvious to try", but rather was based on the fact that the prior art clearly taught the benefits of incorporating cells, including bone marrow cells, into bone grafts prior to implantation, and also provided examples of successful embodiments of doing such.

In response to Applicants' argument that claim 20 and dependents thereof now *optionally* require the cells to incorporated into the ceramic material via centrifugal force or under increased or reduced pressure, it is noted that the method of Muschler, relied upon as disclosure of means for incorporating the cells into a porous scaffold, involves incorporating the bone marrow aspirate under hydrostatic pressure (increased pressure), therefore, the claim does not involve a non-obvious step.

Finally, in response to applicant's argument that the examiner's conclusion of obviousness is generally based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). The field of bone graft compositions is a highly saturated art; the inventions as currently claimed are not considered to provide patentable distinction over what had already been disclosed in that field at the time the invention was made. Applicants' inventions combine various modifications and improvements which were known, at least individually, in the art, for example pore size, including both macropores and micropores of specified sizes, inclusion of bone marrow cells, application mechanical or electrical stimulation to enhance bone cell growth, etc. Because the art recognized each of these modifications as beneficial for improving osteoinduction and bone tissue growth, the invention as claimed is not considered patentably distinct, but merely an optimized embodiment of what was already known. Based on the desire to provide the most optimal bone graft composite, combination of the various disclosed modifications would have been obvious to one of ordinary skill in the art. It has long been held that "a patent for a combination which only unites old elements with no change in their respective functions ... obviously withdraws what is already known into the field of its monopoly and diminishes the resources available to skillful men." *Great Atlantic & Pacific Tea Co.* v. *Supermarket Equipment Corp.*, 340 U.S. 147, 152 [87 USPQ 303] (1950). The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results; in order to dispute that the claimed composition yields more than predictable results, Applicants are required to submit evidentiary showing of unexpected properties specific to the claimed ranges, degrees of porosity, and methods of making, which they feel renders their invention patentably distinct.

Duplicate Claim Warning

Applicant is advised that should claims 9 or 10 be found allowable, claims 14 and 15 will be objected to under 37 CFR 1.75 as being substantial duplicates thereof, respectfully. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). It appears claim 14 has been erroneously amended to depend from claim 8, thereby making it identical to claim 9; it appears claim 14 should depend from amended claim 13. Examination has been conducted as such.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 8-10, 13-15, 20-25 and 27 stand rejected under 35 U.S.C. 103(a) as being unpatentable over de Bruijn et al (EP 0987032), in view of Hakamazuka et al (JP 01-108143), Muschler (WO 99/59500), and Klein-Nulend et al (J Cell Physiol, 1995).

Applicants claims, as amended, are directed to an artificial bone material comprising a porous ceramic consisting of beta-tricalcium phosphate and at least one bone marrow cell incorporated into the porous ceramic, wherein the porous ceramic has a total porosity of 60-90%; wherein the porous ceramic includes interconnected macropores of size from 50 um to 1,000 um, or from 100um to 500 um, which macropores constitute between 30-70% of the total porosity, and micropores of size 2 um or less or from

1 um to 0.1 um, which micropores constitute between 10-40% of the total porosity. Applicants also claim a method for producing such artificial bone materials.

As previously set forth, porous ceramic scaffolds used for generating artificial bone are known in the art. The current claims recite various modifications, such as optimized pore sizes, optimized degrees of porosity, inclusion of bone marrow cells, and inclusion of cell growth factors, all of which were also known in the art to improve the osteoinductive capacity of bone graft materials. While Applicants have argued that the modifications as set forth in the rejection of record would have been non-obvious, stating the Examiner relied on impermissible hindsight to arrive at the claimed combinations, the rejections are maintained on the basis that the claimed inventions merely recite optimized embodiments of what was already known in the art. The disclosure of each modification to the basic bone graft material (represented by de Bruijn et al), motivation to perform each modification, and reasons why one of ordinary skill in the art would have had a reasonable expectation of successfully making such modifications, have also been provided:

De Bruijn et al is relied upon for their disclosure of a basic porous ceramic material: de Bruijn et al teach such porous ceramic materials suitable for use as bone graft materials, as said materials exhibit both biocompatibility and biodegradability. Specifically de Bruijn et al disclose beta-tricalcium phosphate as a preferred ceramic material (See de Bruijn et al, col. 2, ln 20-25).

With regards to the porosity, de Bruijn et al disclose their beta-tricalcium phosphate scaffolds exhibits macro- and microporosity, wherein the macropores preferably have a size of between 0.2 mm and 1.0 mm (200um to 1000 mm), and wherein the micropores preferably have a size of between 0.05 um and 20 um. de Bruijn et al teach the macro- and micropores are interconnected, and the overall porosity is between 20% and 90%, preferably between 40% and 70% (See de Bruijn et al, col. 2, ln 26-46). de Bruijn et al do not disclose the specific breakdown of pore volume percentage represented by the macropores and the micropores; however, such is considered a result effective variable that would be

routinely optimized by the artisan of ordinary skill (Claims 8, 13 and 20). The provision of *both* macro- and micropores is taught by de Bruijn et al to enhance bone tissue formation (See de Bruijn et al, col. 2, ln 38-46); because the pore size(s) is directly related to the size of the ceramic particles used, manipulation of the particle sizes, to produce a material with optimized macropore to micropore ratio would have been a matter of routine optimization. Therefore, de Bruijn et al have disclosed a beta-tricalcium ceramic material that exhibits both macro- and microporosity, wherein the size of the macropores and micropores either lay within the ranges currently claimed by applicant, or significantly overlap with the claimed ranges; as such it is not inventive to discover the optimum or workable ranges by routine experimentation. *In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235(CCPA 1955).* Furthermore, because pore size, the degree of porosity, and the ratio of macropores to micropores are all result effective variables, as they all directly effect the final overall porosity and ability of cells and blood to infiltrate establish new tissue within the scaffold material, these variables would be routinely optimized by the artisan of ordinary skill (Claims 8, 13, 21, 22).

With regards to inclusion of bone marrow cells within the artificial bone material, it is noted that de Bruijn et al do not add cells to their scaffolds *ex vivo*, but rather implant the scaffolds in an acellular state so that natural bone forming cells may invade and colonize the scaffolds *in vivo*. While de Bruijn et al do report some success regenerating bone *in vivo* in this manner, it alternatively would have been obvious to one of ordinary skill in the art, at the time the invention was made, to colonize the scaffold of de Bruijn et al *ex vivo* with cells prior to implantation. Clearly in situations where the intent is to regenerate or repair bone defects, inclusion of cells in the implant is desirable, as the cells express additional growth factors, and reduce the need for chemotaxis of autologous osteoblast progenitor cells to the defect site, thus one of ordinary skill in the art would have been motivated to culture cells on the scaffold of de Bruijn et al. One would have expected success in culturing cells on the scaffold of de Bruijn et al to form an improved artificial bone material for implantation because methods of culturing

cells, specifically bone marrow cells, on ceramic scaffolds for the purpose of artificial bone formation were known in the art, see for example, Muschler. Muschler teaches methods for delivering and culturing cells, specifically cells from bone marrow aspirate obtained from a patient, onto an implantable scaffold to form an artificial bone graft (See Muschler, Pg. 2, ln 20-27). Muschler teaches the scaffold may further have growth factors which contribute to osteogenesis, including bone morphogenic proteins, fibroblast growth factors, insulin-like growth factors, and platelet-derived growth factors (See Muschler, Pg. 5, ln 1-6). (Claims 8-10, 13-15, 21-23, 27).

With regards to methods of producing such porous ceramic scaffolds, such as that of de Bruijn et al, de Bruijn et al disclose the ceramic beta-tricalcium phosphate scaffold can be produced by sintering (See de Bruijn et al, col. 3, ln 6-14), further detail on the production process is found in Hakamazuka et al, where they specifically teach synthesizing tricalcium phosphate via a mechano-chemical process, then molding a slurry of calcined and ground synthetic TCP and an aqueous solution of ammonium polyacrylate, drying, and sintering at high temperatures (See Hakamazuka et al, abstract). Thus, in addition to the teachings of de Bruijn et al, it would have been obvious to one of ordinary skill in the art to look to Hakamazuka et al for additional guidance on the specifics of forming a beta-tricalcium scaffold, as both references are concerned with formation of beta-tricalcium ceramics for use in bone regeneration. Because both references are directed to solving the same problem, and involve the same process of sintering, one would expect success following the more explicit teachings of Hakamazuka et al to produce a porous beta-tricalcium scaffold useful in the method of de Bruijn et al. (Claim 24). Again, Muschler et al is referenced for their disclosure of means and methods for introducing bone marrow cells into a porous ceramic material, specifically under hydrostatic pressure (See Muschler et al, Pg. 6, ln 20-24) (which applicants call incorporating the bone marrow cells into the ceramic under increased pressure); thus means and methods for incorporating the at least one bone marrow cell into the pores of the ceramic

scaffold *ex vivo* would have been obvious to the artisan of ordinary skill at the time the invention was made. (Claims 20-24, 27).

Finally, with regards to application of electric or mechanical stimulation to the bone marrow cell during the incubation within the scaffold, it is maintained that in order to further optimize the artificial bone material of de Bruijn et al, it would have been further obvious to one of ordinary skill in the art to subject the cell-seeded scaffold to mechanical loading (mechanical stimulation). It was known at the time the invention was made that application of mechanical strain on bone cells affects the growth and development of the tissue. Specifically, Klein-Nulend et al disclose application of intermittent hydrostatic compression by 13 kPa to *in vitro* mouse calvariae increases bone formation and decreases bone resorption, as well as affects the production of local growth factors (See Klein-Nulend et al, Pg. 116, col. 1). Therefore, in order to increase bone formation, for the purpose of providing the most suitable bone material for implantation, one of ordinary skill would have been motivated to apply mechanical stimulation to the cells during the culture period; one would have expected success because Klein-Nulend et al provide evidence of improved bone tissue quality with such stimulation. (Claim 25).

Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH

shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Allison M. Ford whose telephone number is 571-272-2936. The examiner can normally be reached on 7:30-5 M-Th, alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Leon B Lankford, Jr
Primary Examiner
Art Unit 1651